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In re Application of: Myriam GOLEMBO et al.	Confirmation No.: 3940
Application No.: 10/664,605	Group Art Unit: 1649
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For: METHOD AND COMPOSITION FOR TREATMENT OF SKELETAL DYSPLASIAS	Attorney Docket No.: 81408-4300

SUBMISSION OF PRIORITY DOCUMENT

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Sir:

Applicants have claimed priority under 35 U.S.C. § 119 of Israeli Application No. 00142118 filed March 20, 2001. In support of this claim, a certified copy of said application is submitted herewith.

No fee or certification is believed to be due for this submission. Should any fees be required, however, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814.

Respectfully submitted,

5-23-06
Date

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212-294-3311

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מספר: NUMBER	
142118	תאריך: Date
20 -03- 2001	הוקדם/ נדחה ANTE/POST-DATED

בקשה לפטנט
Application For Patent

אני, (שם המבקש, מענו ולגבי גוף מאוגד – מקום ההתאגדות)
I (Name and address of applicant, and in case of body corporate-place of incorporation

PROCHON BIOTECH LTD.
an Israeli company of
P.O. Box 1482
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פרוכון ביוטק בע"מ
(חברה ישראלית)
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ממציאים: מרים גולמבו, אבנר יאיון

By the law and assignment

בעל אמצאה מכח

שמה הוא

of an invention the title of which is

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(Hebrew)

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METHOD AND COMPOSITION FOR TREATMENT OF SKELETAL DYSPLASIAS

(English)

hereby apply for a patent to be granted to me in respect thereof.

מבקש בזאת כי ינתן לי עליה פטנט

*בקשה חלוקה- Division of Application	*בקשה פטנט מוסף- Addition Application for Patent	* דרישה דין קדימה Priority Claim		
מבקשת פטנט Application from No מס dated מיום	לבקשה/לפטנט to Patent/Application No מס dated מיום	מספר / סימן Number / Mark	תאריך Date	מדינת האגוד Convention Country
יפוי כח: כללי / מיוחד – רצוף בזה / עוד יוגש to be filed later / attached – P.O.A.: general / individual filed in case הוגש בענין				
המען למסירת מסמכים בישראל Address for service in Israel WEBB, BEN-AMI & ASSOCIATES P.O. Box 2189 Rehovot 76121				
Signature of Applicant חתימת המבקש For the applicant: PRO/011		היום This 20 בחודש of March שנת the year 2001		
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שיטה ותכשיר לטיפול בדיספלזית שלד

METHOD AND COMPOSITION FOR TREATMENT OF SKELETAL DYSPLASIAS

PROCHON BIOTECH LTD.

METHOD AND COMPOSITION FOR TREATMENT OF SKELETAL DYSPLASIAS

FIELD OF THE INVENTION

The present invention relates to treatment of skeletal dysplasias, such as achondroplasia, and in particular to pharmaceutical compositions for bone elongation in abnormal bone growth comprising natriuretic peptides or natriuretic factors.

BACKGROUND OF THE INVENTION

Endochondral ossification is a fundamental mechanism for bone formation, whereby cartilage is replaced by bone. Endochondral ossification requires the sequential formation and degradation of cartilaginous structures that serve as molds for the developing bones. Longitudinal bone growth is determined by the process of endochondral ossification in the cartilaginous growth plate, which is located at both ends of vertebrae and long bones.

During fetal life and until the end of puberty, longitudinal bone growth takes place via endochondral ossification of the growth plate located at the epiphyses (ends) of long bones. The growth plate is divided into several zones of cartilage forming cells, or chondrocytes, with distinct patterns of gene expression. In the Reserve Zone, cells are small and relatively inactive. In the adjacent Proliferative Zone, chondrocytes proliferate, arrange themselves in columns and

eventually undergo hypertrophy. In the lower Hypertrophic Region towards the cartilage-bone junction, cells are big and highly active but exhibit no further cell division. The matrix surrounding the hypertrophic cells calcifies and the lowermost cells undergo programmed cell death. Cell death is accompanied by the removal of the cartilaginous matrix and its replacement by bone through the concerted action of recruited bone cells, namely osteoclasts and osteoblasts.

The process of endochondral ossification is the result of the concerted action of several signaling pathways. The signallung pathway triggered by activation of Fibroblast growth factor (FGF) receptors have been shown to be involved in several stages of limb and bone development. The FGF receptor 3 (FGFR3) plays a central role in endochondral ossification as demonstrated by the fact that several mutations at various positions in this receptor result in skeletal dysplasias such as Achondroplasia .

Achondroplasia is the most common form of short-limbed dwarfism occurring with a frequency of 1:20000 live births. Patients show characteristic shortening of proximal long bones (rhizomelia), relative macrocephaly, depressed nasal bridge and lumbar lordosis.

Achondroplasia is mainly caused by a Gly380Arg mutation in the transmembrane domain of the FGFR3 and is transmitted in an autosomal dominant fashion (Shiang et al. (1994) Cell 78: 335-342 and Rousseau et al. (1994) Nature 371: 252-254). A Gly375Cys mutation has also been reported in some Achondroplaia patients. These mutation affects the process of endochondral

ossification by inhibiting proliferation and delaying maturation of chondrocytes in the growth plate cartilage of long bones, resulting in decreased elongation.

FGFR3 has an inhibitory role in bone elongation as demonstrated by the fact that mice lacking this receptor exhibit a phenotype of skeletal overgrowth.

Natriuretic peptides are known for their role in cardiovascular homeostasis, diuresis, natriuresis and vasodilation. Three isoforms constitute this family: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). While ANP and BNP are circulating peptides produced by the atria and the ventricle respectively, CNP is hardly found in the circulation and is mainly produced in the brain, in vascular endothelial cells and other tissues where it is supposed to work in an autocrine/paracrine manner (Chen and Burnett, (1998) J.Cardiovasc.Pharmacol. 32 Suppl 3:S22-8).

Natriuretic peptides effect their biological role through two receptors: NPR-A and NPR-B. These receptors have cytoplasmic guanylyl cyclase domains, which are activated upon ligand binding and lead to accumulation of intracellular cGMP. Some of the effects of cGMP are mediated through two known protein kinases: cGMP-dependent protein kinase I and II. The peptides bind the receptors with different affinities: ANP$\geq$BNP>>CNP for NPR-A and CNP> ANP$\geq$ BNP for NPR-B. The tissue distribution of each receptor is different. While NPR-A is expressed in vasculature, kidney and adrenal glands, NPR-B is mainly expressed in the brain.

A third receptor, NPR-C has no cytoplasmic guanylyl cyclase domain and is generally considered to be a clearance receptor for removing natriuretic

peptides from the circulation, though some other biological functions have been attributed to it (Murthy and Makhlouf. (1999) JBC 274:17587-17592). This is the most widely distributed receptor and is expressed in almost all the tissues that express a guanylyl cyclase receptor.

Natriuretic peptides are further cleared from the circulation by degradation. The peptides are cleaved at specific sites, by the neutral endopeptidase 24.11 (NEP) which is found in endothelial cells covering the vascular walls. BNP is more resistant to this degradation while ANP and CNP are readily degraded by this enzyme. Inhibition of the endopeptidase by inhibitors including for instance the compounds thiorphan or candoxatril (Ohbayashi et al. (1997) Clin. Exp. Pharmacol. Physiol. 25: 986-91; Brandt et al. (1997) Hypertension 30: 184-90), increases the concentration of the endogenous or administered peptides in the circulation.

Transgenic mice, over-expressing BNP show skeletal phenotype characterized by overgrowth of the axial and appendicular skeleton (Suda et al. (1998) PNAS 95: 2337-2342). Moreover, mice that are null mutants for the clearance receptor, NPR-C, exhibit a similar skeletal overgrowth, consistent with a role for the local modulation of natriuretic peptides levels by NPR-C (Matsukawa et al. (1999) PNAS 96: 7403-7408). CNP and its specific receptor, NPR-B have been shown to be expressed in the proliferating zone of the growth plate in fetal mouse tibia while NPR-C has been shown to be expressed in the region of hypertrophic chondrocytes and in osteoblasts (Yamashita et al. (2000) J.Biochem 127: 177-179).

Furthermore, *ex vivo* experiments with fetal bone organ culture from wild type anmals have shown that CNP, more than BNP and ANP, can induce bone elongation (Yasoda et al. (1998) J. Biol. Chem. 273: 11695-11700, Mericq et al. (2000) Pediatric Research 47: 189-193).

While much is known about the components of signaling pathways that contribute to the process of endochondral ossification, little is known about the complex interactions between them that coordinate longitudinal bone growth.

Nowhere in the background art is it taught or suggested that natriuretic peptides may be useful for the treatment of skeletal dysplasias of any type, nor of achondroplasia in particular.

SUMMARY OF THE INVENTION

The present invention provides a method and composition for treating skeletal dysplasias such as achondroplasia. The method and composition of the invention effect bone elongation, inter alia, by increasing the size of the hypertrophic zone of the bone, specifically of limb bones.

The invention provides the use of natriuretic peptides (NP) in effecting bone elongation and treating skeletal dysplasias.

The term "natriuretic peptides" or "NP" as referred to herein relates to any of the three isoforms, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) and to any functional derivatives thereof.

The method of the invention for treating skeletal dysplasias includes the step of administering to a patient an effective amount of an NP. In one embodiment of the invention the natriuretic peptide is CNP. The method may further include a step of administering to the patient an inhibitor of neutral endopeptidase 24.11 (NEP). Suitable compounds for inhibiting NEP are known in the art, including but not limited to thiorphan or candoxatril. Administration of such an inhibitor of neutral endopeptidase may be performed either separately or simultaneously with the administration of NP.

It may also include administering an inhibitor of the clearance receptor NPR-C either alone or in conjunction with administration of NP.

Administration of NP to a patient can be achieved by any suitable route of administration, including but not limited to injecting NP to the patient, inhalation, or implantation of a depot into the patient. NP may further be administered by an osmotic pump, such as an Alzet pump. The osmotic pump can be implanted subcutaneously, or at any other appropriate site. Preferred sittes may be close to the target site of action namely in proximity to the lon bones of the limbs.

A further method of administration may be implantation of NP secreting cells. Methods for implantation of NP secreting cells include encapsulation of the cells in any immunologically inert matrix. One non-limitative example of such a matrix is an alginate-polylysine-alginate (APA) complex encapsulating the cells. These methods of administration and other known methods may be utilized alone or in combination for treating skeletal dysplasia.

The present invention further provides a composition for treatment of skeletal dysplasias, such as achondroplasia. The composition includes an NP and any pharmaceutically acceptable diluent or carrier thereof. According to one currently more preferred embodiment of the invention the natriuretic peptide is BNP. According to one currently most preferred embodiment of the invention the natriuretic peptide is CNP. The composition may further include any substance, molecule or vehicle capable of increasing the NP stability in vivo. For example the composition may include an inhibitor of neutral endopeptidase 24.11 (NEP), including but not limited to thiorphan or candoxatril.

The composition may be in any form suitable for being administered to a patient, including but not limited to in liquid form or in suspension.

Also provided is a composition for treatment of skeletal dysplasias that includes NP secreting cells encapsulated within an immunologically inert matrix. One currently preferred embodiment includes NP secretingcells encapsulated in an alginate-polylysine-alginate (APA) complex and a suitable carrier thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the drawings in which:

Figure 1 shows the growth rate curves for the different animals in the ex vivo experiment; and

Figure 2 shows the interpolation of the growth rate curves of Fig. 1.

DETAILED DESCRIPTION OF THE INVENTION

Achondroplasia is characterized, inter alia, by shortening of proximal long bones. In humans the bone growth plate is active until puberty and and bone growth is thus achieved until puberty. Thus, treatment aimed at bone elongation, for example, by increasing the size of limb bone hypertrophic zone, would be advantageous during this period.

Treatment of skeletal dysplasias such as achondroplasia, includes treating a shortened bone with NP. The bone may be treated by administering to a patient an effective amount of NP. The amount of the active ingredient administered will be determined by the attending physician and is generally proportional to the patient's weight

According to the present invention it is now disclosed that NP can induce bone elongation in situation of abnormal bone growth such as those typical of skeletal dysplasias.

The role and use of NPs in bone elongation in situations of abnormal bone growth and in the treatment of skeletal dysplasias, such as achondroplasia, is demonstrated in the following examples and experiments.

Ex Vivo Experiment

Femurs derived from a mouse Achondroplasia model (Ach369 knock-in) were dissected from P0 wild type, heterozygote and homozygote littermates and cultured in the presence of natriuretic peptides for 24 days.

Protocol for bone culture

Femora are derived from Ach 369 homozygote, heterozygote or wt littermates. (Ach369 mice are knock-in mice carrying the mutation for achondroplasia Gly→Cys at position 369 homologous for the human position 375).

Two femora from newborn animals, aged P0, are dissected and cleaned from surrounding muscle.

The femora are incubated (one/well) in serum-free media consisting of :

MEM ALPHA medium (without ribonucleosides and deozyribonucleasides, GIBCO BRL);

0.2% BSA (fraction V, Sigma);

Penicillin-streptomycin-nyastatin solution (Beit Haemek, Israel); and

1mM b-glycerolphosphate disodium.

Femora length was measured using an eyepiece micrometer in a dissecting microscope.

CNP was added to culture medium at indicated concentration.

Medium was changed and femora length measured every 3 days.

Results

It is known from *ex vivo* experiments with fetal bone organ culture from wild type (normal) animals that CNP, more than BNP and much more than ANP, can induce bone elongation. According to the present invention it si now shown that natriuretic peptides can induce longitudinal growth of Achondroplasia-derived bones.

CNP increased the total longitudinal growth of femurs derived from Ach369 and wild type mice compared to vehicle treated animals.

Figs. 1 and 2 depict the growth rate curves for the different animals in the experiment. The growth rate curve shows two different stages of growth: an initial stage (days 0-3) in which growth is quick and is most affected by the presence of natriuretic peptides and a second slower linear rate. Interestingly, at this stage, femurs derived from homozygote Ach animals respond better to CNP than femurs derived form heterozygote animals while bones derived from wt animals are very slightly influenced by CNP. This is summarized in Table 1.

Genotype	**Treated/untreated growth rate**
Ach369 homozygote	2.28
Ach369 heterozygote	1.7
Wild type	1.07

This suggests that Achondroplasia derived rudiments have got the capacity to respond to CNP for a longer period of time. Fig. 1 shows that with time, NP treated femurs from Ach homozygote pups become longer than those from untreated Ach heterozygote mice and a plateau has not been reached. In fact, the change in growth rate was more marked in femurs derived from homozygote animals than in those from heterozygote animals and finally in wt animals.

Natriuretic peptides lead to an increase in the size of hypertrophic zone

Most of the elongation induced by natriuretic peptides observed in bone culture results from epiphyseal growth and not from elongation of the mineralized diaphysis. Morphological analysis of the cellular composition of the growth plate in treated samples revealed that there is a relative increase in the size of the proliferative region and a marked increase in the size of the hypertrophic zone. This could be due to an increase in the pool of growth plate chondrocytes which subsequently differentiate into hypertrophic cells, or to "accelerated" maturation which would also lead to an increase in bone length.

BNP specific for mouse was synthesized and labeled with biotin. This BNP was also tested in bone culture on bones derived from Achondroplasia and it could also induce bone elongation. Nevertheless, BNP was used at a higher concentration than CNP.

Histological analysis of the distribution of biotinylated BNP in the growth plate shows that it is apparent both in proliferative and in hypertrophic cells. Recent studies have shown the distribution of the NP receptors in the growth plate: NPR-B is expressed in proliferative cells while NPR-C is expressed in hypertrophic cells (Yamashita et al. (2000) J.Biochem 127: 177-179). Therefore, BNP could exert its effect on bone growth either by stimulating the activity of NPR-B or by blocking the clearance of the endogenous peptide, CNP, through NPR-C.

In Vivo Experiments

IP administration of drugs to Achondroplasia pups

The fastest growth period for mice is during the first month of life therefore, by initiating the experiments as early as possible it is expected to influence growth the most. One disadvantage is the fact that at this age, there is a limit on volume delivered. Delivery of drug can not be performed intravenously (IV) or by implantation of a continuous delivery device like a pump.

Animals

Heterozygote mice for the Achondroplasia mutation, aged P4-P5, weighing approximately 3.5 gr.

Animals are randomly separated into groups of 3 animals/group and ear marked. Animals are distributed 6-7 individuals/cage with one foster mother.

Materials and procedures

Animals are injected daily with drug intraperitoneally (IP) in a volume not exceeding 50μl. This volume can be increased proportionally to weight increase.

Animals are weighed and the tail length is measured on day 0 and every 2 days thereafter

The treatment is continued for 2 weeks

At the end of the administration period animals are sacrificed and skeletal elements are measured and analyzed by histology.

CNP is administered at a concentration of 10^{-7}M and 10^{-6}M during 2 weeks. In all experiments in mice CNP was diluted in 1x PBS.

Administration of drugs to Achondroplasia model mice by continuous release from Alzet pumps

Release of drugs by osmotic pumps provides a continuous supply and a constant amount of circulating drug. Furthermore, it enables directed release of the drug closer to the target site. Nevertheless, this procedure can only be performed in older mice.

Animals

Heterozygote mice for the Achondroplasia mutation, aged P12-P14, weighing approximately 10 gr.

Animals are randomly separated into groups of 3 animals/group and ear marked. Animals are distributed 6-7 individuals/cage with one foster mother.

Materials and Procedure

The Alzet pumps used have a total volume of 100µl and a release constant of .25 µl/hour during 14 days.

Pumps are filled with appropriate drug and calibrated for4-6 hours

Pumps are implanted subcutaneously (SC) on the back of anesthetized mice and the contents are directed with a catheter to the femoral artery of one hindlimb.

Mice are monitored for recovery and returned to mothers.

Mice are weighed and measured every 2 days.

At the end of the administration period animals are sacrificed and skeletal elements are measured and analyzed by histology.

This experiment was performed with a concentration of 10^{-4}M of CNP in pump to obtain a concentration of 10^{-7}M in the blood stream. In all experiments in mice CNP was diluted in 1x PBS.

Implantation of alginate encapsulated cells that secrete CNP

Transfected NIH-3T3 fibroblasts with mouse CNP gene were tested for CNP is production and secretion.

The cells were encapsulated in APA (alginate-polylysine-alginate) complex and were implanted intraperitoneally (IP) into P5 mice (Ach369 and wt).

Mice are weighed and tail length measured every 2 days for 3 weeks.

Administration of drugs together with an NEP inhibitor to Achondroplasia model mice by continuous release from Alzet pumps

The NP have a short half-life in the circulation, probably due to the activity of the neutral endopeptidase.

An experiment is performed in which CNP is administered at 10^{-4}M in pump to obtain a concentration of 10^{-7}M in blood stream together with thiorphan (NEP inhibitor) at a concentration of 10 mg/ml in pump (10 μg/ml blood stream) for 2 weeks. Administration is done by using an Alzet pump that releases its contents subcutaneous. The same animals are injected with extra CNP daily, IP, together with 0.1% BSA at a concentration of 10^{-7}M.

A similar experiment is performed with biotin labelled BNP that was administered to animals which also received thiorphan. BNP is at 10^{-4}M in pump

to obtain a concentration of 10^{-7}M in blood stream, and 10^{-7}M is injected daily as for CNP.

In a similar manner, any combination of NPs with compounds that contribute to NP stability in the circulation can be administered to a patient for efficient bone elongation and/or treatment of skeletal dysplasias. Such combinations may include a mixture of CNP and BNP, NPs in combination with peptidase inhibitors, NPs in combination with NPR-C antagonists, and so on.

It will be evident to the skilled artisan that administration of NPs according to the principles of the present invention can be performed by any suitable route of administration, utilizing any suitable pharmaceutically acceptable carrier or diluent. Under certain circumstances specific formulations that enable or enhance targetting of the active principle to the bone or growth plate may be utilized such as but not limited to use of the NPs in combination with vehicles such as liposomes, microemulsions, microcapsules, microspheres, and the like. It is also intended according to the principles of the present invention that molecules may be conjugated to the active principle (NP) to prolong the halflife or in order to enhance targetting. Candidate moleculesinclude Antibody peptidesm hydroxyapatite, glucosamine, collagen especially collagen type X, polyGlu or polyAsp and other molecules having affinity for the growth plate.

It will be appreciated that many improvements may be achieved by stabilization of the NP or otherwise achieveing a prolonged half life or improved phamacokinetic profile. For example, functional derivatives of NPs having enhanced stability in vivo, such as peptides having altered sequences or

configurations, may be administered for treatment of skeletal dysplasias and/or bone elongation.

Further, cells can be engineered to produce and secrete functional derivatives of NPs having enhanced stability in vivo and these cells may be encapsulated in APA (alginate-polylysine-alginate) complex and implanted intraperitoneally for treatment of skeletal dysplaisias and/or bone elongation.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather the scope of the present invention is defined only by the claims which follow:

CLAIMS

1. A method for increasing the size of a bone hypertrophic zone in abnormal bone growth.comprising the step of treating the bone with an effective amount of at least one natriuretic peptide, or variants thereof.

2. The method according to claim 1 wherein the at least one natriuretic peptide is CNP.

3. The method according to claim 1 wherein the at least one natriuretic peptide is BNP.

4. The method according to claim 1 further comprising inhibiting the natriuretic peptide clearance receptor.

5. The method according to claim 1 wherein the bone is a limb bone.

6. The method according to claim 5 wherein the limb bone is an achondroplasic bone.

7. A method for bone elongation in abnormal bone growth, comprising the step of treating the bone with an effective amount of at least one natriuretic peptide, or variants thereof..

8. The method according to claim 7 wherein the at least one natriuretic peptide is CNP.

9. The method according to claim 7 wherein the at least one natriuretic peptide is BNP.

10. The method according to claim 7 further comprising inhibiting the natriuretic peptide clearance receptor.

11. The method according to claim 7 wherein the bone is a limb bone.

12. The method according to claim 11 wherein the limb bone is an achondroplasic bone.

13. Use for the preparation of a medicament for treating skeletal dysplasia of at least one natriuretic peptide.

14. Use according to claim 13 wherein the at least one natriuretic peptide is CNP.

15. Use according to claim 13 wherein the at least one natriuretic peptide is BNP.

16. Use according to claim 13 wherein the skeletal dysplasia to be treated comprises achondroplasia.

17. A pharmaceutical composition for bone elongation comprising at least one natriuretic peptide and a carrier thereof.

18. A pharmaceutical composition according to claim 17 wherein the at least one natriuretic peptide is CNP.

19. A pharmaceutical composition according to claim 17 wherein the at least one natriuretic peptide is BNP.

20. A method for treatment of skeletal dysplasias comprising the step of administering to a patient a therapeutically effective amount of at least one natriuretic peptide.

21. The method according to claim 20 wherein the at least one natriuretic peptide is CNP.

22. The method according to claim 20 wherein the at least one natriuretic peptide is BNP.

23. The method according to claim 20 further comprising the step of administering to the patient an inhibitor of neutral endopeptidase 24.11 .

24. The method according to claim 23 wherein the inhibitor of neutral endopeptidase is thiorphan or candoxatril.

25. The method according to claim 23 wherein the step of administering to the patient an inhibitor of neutral endopeptidase is performed simultaneously with the step of administering to a patient an effective amount of at least one natriuretic peptide.

26. The method according to claim 20 wherein the skeletal dysplasia is achondroplasia.

27. A composition for treatment of skeletal dysplasias comprising at least one natriuretic peptide and a pharmaceutically acceptable carrier or diluent.

28. A composition according to claim 27 wherein the at least one natriuretic peptide is CNP.

29. A composition according to claim 27 wherein the at least one natriuretic peptide is BNP.

30. A composition according to claim 27 further comprising an inhibitor of neutral endopeptidase.

31. A composition for treatment of skeletal dysplasias comprising natriuretic peptide secreting cells encapsulated within an inert matrix.

32. A composition for treatment of skeletal dysplasias comprising natriuretic peptide secreting cells encapsulated within an alginate-polylysine-alginate complex and a carrier thereof.

For the Applicant,

Cynthia Webb

Cynthia Webb, Ph.D.
Patent Attorney
Webb, Ben-Ami & Associates
PRO/011

Abstract

The present invention discloses pharmaceutical compostions for the treatment of skeletal dysplasias, comprising as an active ingredient at least one natriuretic peptide. Unexpectedly, it has been shown that the natriuretic factors may be effective for bone elongation in situations of abnormal bone growth especially for achondroplasia. The effects of the natriuretic peptide may be furhther enhanced by prolonging its residence time or action at the target site.

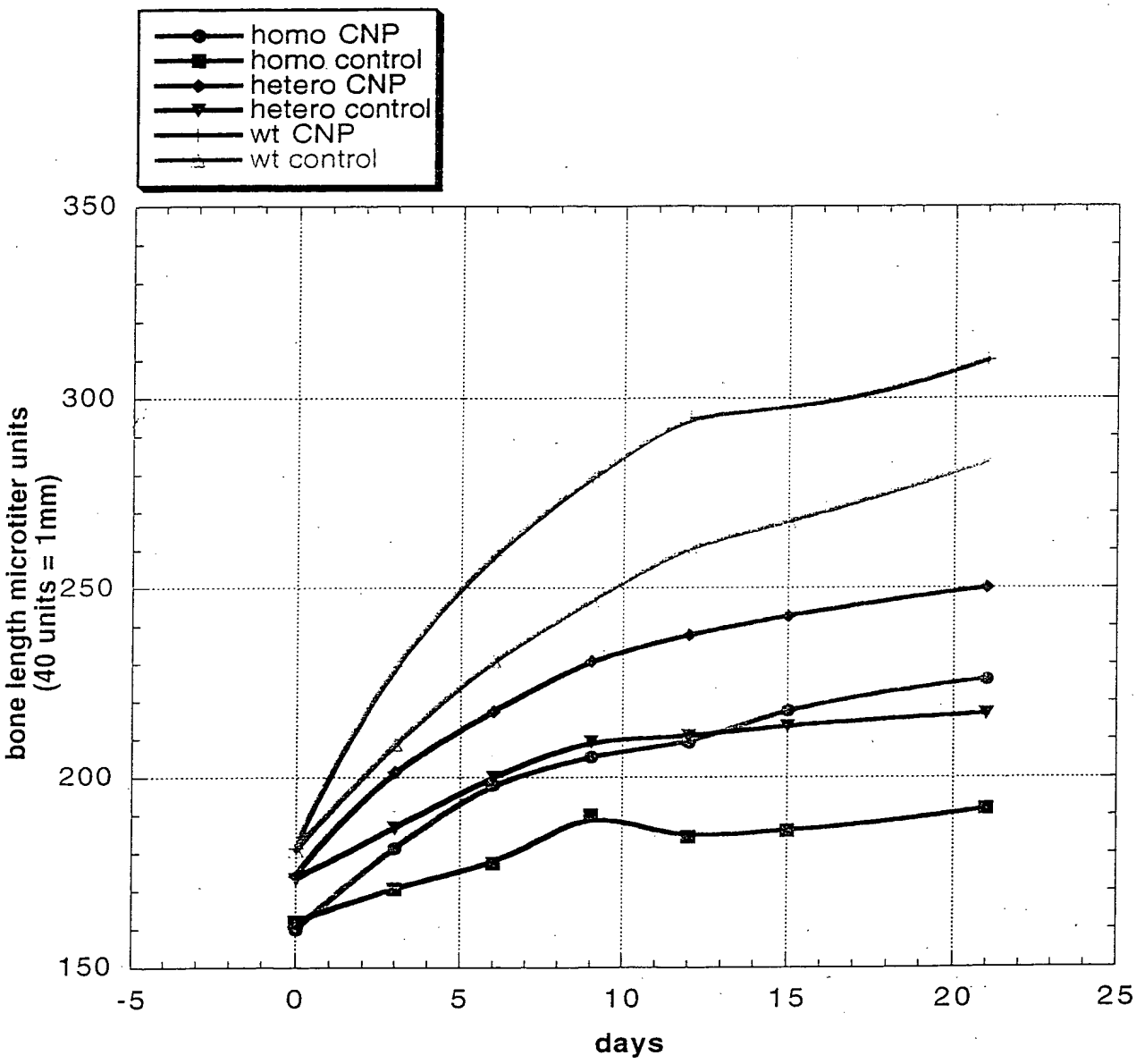
homo CNP
homo control
hetero CNP
hetero control
wt CNP
wt control
350
300
250
200
150
bone length microtiter units
(40 units = 1mm)
-5
0
5
10
15
20
25
days

FIGURE 1

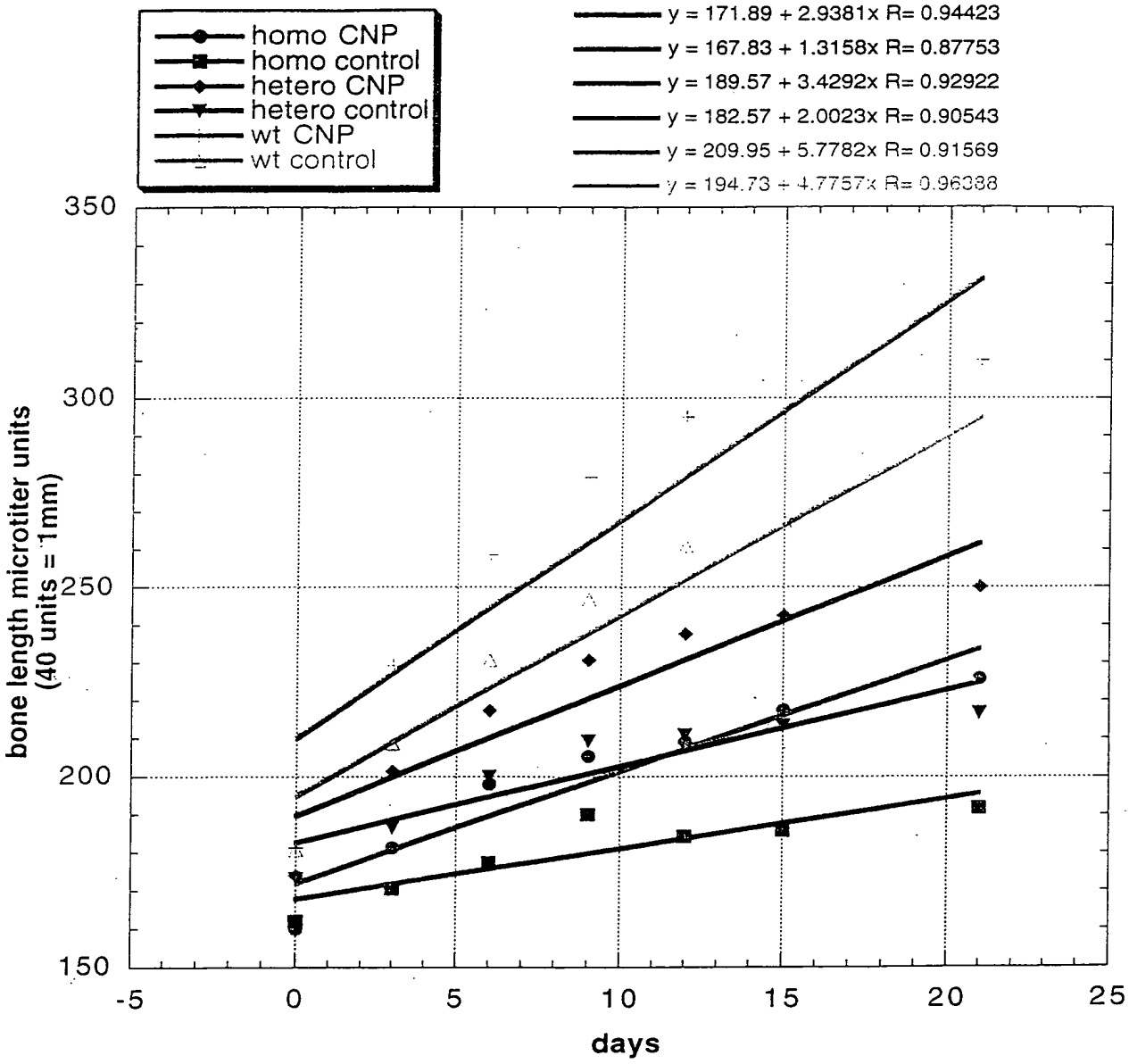
homo CNP
homo control
hetero CNP
hetero control
wt CNP
wt control
y = 171.89 + 2.9381x R= 0.94423
y = 167.83 + 1.3158x R= 0.87753
y = 189.57 + 3.4292x R= 0.92922
y = 182.57 + 2.0023x R= 0.90543
y = 209.95 + 5.7782x R= 0.91569
y = 194.73 + 4.7757x R= 0.96088
bone length microtiter units
(40 units = 1mm)
350
300
250
200
150
-5
0
5
10
15
20
25
days

FIGURE 2